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Research Paper

Diagnosis Of Persistent Infection In Prosthetic Two-Stage Exchange: PCR analysis of Sonication fluid From Bone Cement Spacers

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Abstract

Introduction: When treating periprosthetic joint infections with a two-stage procedure, antibiotic-impregnated spacers are used in the interval between removal of prosthesis and reimplantation. According to our experience, cultures of sonicated spacers are most often negative. The objective of our study was to investigate whether PCR analysis would improve the detection of bacteria in the spacer sonication fluid.

Methods: A prospective monocentric study was performed from September 2014 to January 2016. Inclusion criteria were two-stage procedure for prosthetic infection and agreement of the patient to participate in the study. Beside tissues samples and sonication, broad range bacterial PCRs, specific *S. aureus* PCRs and Unyvero-multiplex PCRs were performed on the sonicated spacer fluid.

Results: 30 patients were identified (15 hip, 14 knee and 1 ankle replacements). At reimplantation, cultures of tissue samples and spacer sonication fluid were all negative. Broad range PCRs were all negative. Specific *S. aureus* PCRs were positive in 5 cases. We had two persistent infections and four cases of infection recurrence were observed, with bacteria different than for the initial infection in three cases.

Conclusion: The three different types of PCRs did not detect any bacteria in spacer sonication fluid that was culture-negative. In our study, PCR did not improve the bacterial detection and did not help to predict whether the patient will present a persistent or recurrent infection. Prosthetic 2-stage exchange with short interval and antibiotic-impregnated spacer is an efficient treatment to eradicate infection as both culture- and molecular-based methods were unable to detect bacteria in spacer sonication fluid after reimplantation.

Key words: Infection, Two-Stage Exchange, Sonication, Spacer

Introduction

When treating periprosthetic joint infections with a two-stage procedure, antibiotic-impregnated spacers can be used in the interval between implant removal and reimplantation of a new prosthesis. The spacer provides local antibiotics, prevents soft tissues retraction and avoids formation of seroma in the dead space left by the removed prosthesis. However, it may also act as a foreign-body that can be colonized by microorganisms.

In the literature, most studies report cases of positive spacer sonication at the time of second stage procedure from 20% to 50% [1-4]. Nevertheless, according to our experience, cultures of sonicated spacers are always negative. Those results can be explained either by the absence of bacteria, or by the inhibition of bacteria by antibiotics eluted in the

sonication fluid. In our series, antibiotic concentrations of spacer sonicated fluid are high enough to prevent bacteria growth on cultures. The objective in this study was to investigate whether PCR analysis would improve the detection of bacteria in the spacer sonication fluid.

Methods

A prospective monocentric study was performed from September 2014 to March 2016 at the Lausanne University Hospital (CHUV), Switzerland. Inclusion criteria were patients who were operated for a periprosthetic joint infection treated with two-stage exchange and who gave their informed consent to participate in the study. The study was approved by the local ethical committee.

The diagnosis of infection was confirmed either by multiple positive periprosthetic cultures and/or, sonication of the prosthesis at the first stage of the procedure. The threshold of ≥50 CFU was defined as positive cultures, being a sign of infection [5]. Moreover, patients with fistula were considered infected even if all cultures samples were negative.

30 consecutive patients were included: 15 total hip arthroplasties (THA), 14 total knee arthroplasties (TKA), 1 total ankle arthroplasty (TAA). 8 patients were female and 22 were male. Mean age was 66 years old (range 28-85). The bacteria identified were *Staphylococcus epidermidis (8)*, *S. aureus (7)*, *S. capitis (3)*, *Streptococcus dysgalactiae (4)*, *S. milleri (2)*, *S. pneumoniae (1)*, *S. salivarius (1)*, *Enterococcus faecalis (1)*, *Propionibacterium acnes (1)*, *Clostridium celerecrescens (1)* and *Campylobacter fetus (1)*.

At the first stage of the procedure, the prosthesis was removed and was sent for sonication to the laboratory of microbiology [5-6]. Wide debridement was performed collecting at least 2-3 periprosthetic tissues samples which were sent for culture. Then a handmade spacer was formed. For the production of the spacer 40g of the shelf cement containing 0.5g of gentamycin (Palacos G, Hereaus Medical, Berlin, Germany) were handmixed with supplemental 1.2g tobramycin and 2g vancomycin. Empiric intravenous antibiotics were administrated postoperatively followed by specific intravenous antibiotics, once the susceptibility tests were available. Rifampicin was not introduced before the second stage was completed, in order to avoid development of rifampicin-resistant bacteria. A short interval from 2 to 4 weeks was chosen for each case; the best time of reimplantation being decided depending on patient's health condition (for example, the day of the second-stage procedure would be postponed in case of cardiac or diabetic decompensation), local status (acceptable quality of bone or soft tissue at the time of implant removal), pathogen involved (absence of difficult-to-treat microorganisms such as rifampicin-resistant staphylococci, ciprofloxacin-resistant gram-negative bacteria, fungi) and decreasing of CRP and white blood cell count, without any strict cut-off value. There was no antibiotic-free period between the two stages.

At the second stage, the spacer was removed, a wide debridement was performed and the new prosthesis was implanted. At this stage, cultures of 2-3 samples were collected and the spacer was sonicated. For the purpose of the study, Gram strain and three types of PCR were done on sonication fluid on sonication fluid.

Our sonication protocol consists of two minutes at 40kHz using sonication device Bactosonic (Bandelin GmbH, Berlin, Germany). A minimum of phosphate buffered saline (PBS) fluid was poured in the sterile container containing the spacer. The quantity of fluid was depending on the size of the spacer and covered at least 90% of the spacer.

After sonication, a sample of sonication fluid was collected under laminar flow for PCR analysis. One portion of the liquid was centrifugated at a relative centrifugal force of 17.44 g or 10'000 rotations per minute (rpm/min). The pellet was resuspended in PBS fluid.

Unyvero Multiplex-PCRs (Curetis, Germany), broad range bacterial PCRs (16S), were performed on the sonicated spacer fluid. Then *Staphylococcus aureus* and *mecA gene* specific PCRs were used only on sonicated spacer fluid of patients who had primary infection with those specific bacteria (11 patients). The *mecA* gene is a specific gene found in bacteria, either in S. aureus or S. negative coagulase, that determines for resistance to methicilin.

Home-brew developed PCRs specific for *S. aureus* and *mec A gene* were performed in a second step on a subset of specimens that were negative with the broad range bacterial PCRs and the multiplex-Unyvero PCRs system but positive by culture for those specific bacteria in the primary infection.

The PCR analyses were performed during the first 3-4 days after sonication, except for Unyvero Multiplex-PCRs that were performed 2 to 4 weeks after sonication, with samples kept at -80°C between the different stages of the procedure.

Results

At a mean follow-up of 12.8 months (range from 1 to 24 months), we had two persistent infections: one patient infected with *S. epidermidis* and one patient infected with *methicilin-resistant S. aureus (MRSA)*. Four patients had a re-infection (13.3%): one

hematogenous THA infection by *S. aureus* caused by diabetic foot ulcer 9 months later, one hematogenous THA infection by *S. aureus* 5 months later and two cases of persistent serous discharge of wound 1 month after reimplantation (1 THA infection by *E. faecalis* and 1 TKA infection by *E. cloacae)*. As the bacteria identified were different from the first stage procedure, they were treated by debridement, changing of the mobile part and implant retention. Re-infection appeared between 1 and 8 months after reimplantation (mean: 3.5 months).

At reimplantation, Gram strain, cultures of tissue samples and spacer sonication fluid were all negative. Table 1 describes the results obtained with the different PCR methods. Of culture-negative samples, the broad range bacterial PCRs were all negative. However, specific *S. aureus* PCRs (associated with analyses of *mecA* gene) were positive in 5 cases: for *methicilin-resistant negative coagulase Staphylococcus* in two cases, for *methicilin-resistant S. aureus* in two cases and for *methicilin-sensitive S. aureus* in one case. Concerning those five cases, in two cases of primary infection by *methicilin-resistant S. epidermidis*, specific *S. aureus* PCR was positive for the *methicillin-resistant negative coagulase Staphylococcus*. However, one patient did not present a re-infection during the follow-up time of the study and the other patient developed a re-infection at *E. faecalis*. In one case of primary infection by *methicilin-resistant S. epidermidis*, specific *S. aureus* PCR was positive for *methicilin-resistant S. aureus*. However, this patient did not develop a re-infection. In one case of primary infection at *methicilin-resistant S. aureus*, specific *S. aureus* PCR was positive for the same bacteria. However, this patient developed a re-infection at *E. cloacae*. In one case of primary infection by *methicilin-sensitive S. aureus*, specific PCR was positive for the same bacteria. However, this patient did not present a reinfection.

Table 1. Results of PCR analysis

Patients	Implants	Primary infection	At second stage of total arthroplasty replacement				Re-infection
			Tissue cultures	Broad range PCR	Specific S.aureus PCR	Multiplex Unyvero PCR	
1	THR	Streptococcus dysgalactiae	STERILE	NEGATIVE	NA	NEGATIVE	None
2	TKR	S. epidermidis	STERILE	NEGATIVE	NA	NEGATIVE	Persistent infection with cutaneous fistula
3	THR	methicilin-resistant S. epidermidis	STERILE	NEGATIVE	POSITIVE S.aureus / POSITIVE mecA	NEGATIVE	None
4	THR	Propionibacterium acnes	STERILE	NEGATIVE	NA	NEGATIVE	None
5	THR	methicilin-resistant S. epidermidis	STERILE	NEGATIVE	NEGATIVE S.aureus / POSITIVE mecA	NEGATIVE	None
6	THR	S. aureus	STERILE	NEGATIVE	NEGATIVE S.aureus / NEGATIVE mecA	NEGATIVE	Re-infection by S. aureus
7	TKR	S. aureus	STERILE	NEGATIVE	NA	NEGATIVE	None
8	THR	S. epidermidis	STERILE	NEGATIVE	NA	NEGATIVE	None
9	THR	methicilin-resistant S. epidermidis	STERILE	NEGATIVE	NEGATIVE S.aureus / POSITIVE mecA	NEGATIVE	Re-infection by Enterococcus faecalis
10	TAR	Staphylococcus capitis	STERILE	NEGATIVE	NA	NEGATIVE	None
11	TKR	Streptococcus pneumoniae	STERILE	NEGATIVE	NA	S.aureus (+)	None
12	THR	Enterococcus faecalis	STERILE	NEGATIVE	NA	NEGATIVE	None
13	THR	S. aureus	STERILE	NEGATIVE	POSITIVE S.aureus/ NEGATIVE mecA	S.aureus (+)	None
14	THR	S. epidermidis	STERILE	NEGATIVE	NA	S. negative coagulase (+)	None
15	TKR	Streptococcus dysgalactiae	STERILE	NEGATIVE	NA	NEGATIVE	Re-infection by Staph aureus
16	TKR	methicillin-resistant S. aureus	STERILE	NEGATIVE	POSITIVE S.aureus/ POSITIVE mecA	NEGATIVE	Re-infection by Enterobacter cloacae
17	THR	Streptococcus milleri	STERILE	NEGATIVE	NA	S. negative coagulase (+)	None
18	TKR	Streptococcus salivarus	STERILE	NEGATIVE	NA	S. negative coagulase (+) + P. acnes (+)	None
19	TKR	Streptococcus dysgalactiae	STERILE	NEGATIVE	NA	NEGATIVE	None
20	THR	Campylobacter fetus	STERILE	NEGATIVE	NA	NEGATIVE	None
21	TKR	Streptococcus milleri	STERILE	NEGATIVE	NA	NEGATIVE	None
22	TKR	methicillin-resistant S. aureus	STERILE	NEGATIVE	NEGATIVE S.aureus/ NEGATIVE mecA	NEGATIVE	None
23	TKR	methicillin-resistant S. aureus	STERILE	NEGATIVE	NEGATIVE S.aureus/ NEGATIVE mecA	NEGATIVE	Persistent infection with cutaneous fistula
24	TKR	Streptococcus dysgalactiae	STERILE	NEGATIVE	NA	S. negative coagulase (+)	None
25	THR	S. epidermidis	STERILE	NEGATIVE	NEGATIVE S.aureus/ NEGATIVE mecA	NEGATIVE	None
26	THR	Staphylococcus capitis	STERILE	NEGATIVE	NA	NEGATIVE	None

Patients	Implants	Primary infection	At second stage of total arthroplasty replacement				Re-infection
			Tissue cultures	Broad range PCR	Specific S.aureus PCR	Multiplex Unyvero PCR	
27	TKR	Clostridium celerecrescens	STERILE	NEGATIVE	NA	NEGATIVE	None
28	TKR	methicilin-resistant S. epidermidis	STERILE	NEGATIVE	NEGATIVE S.aureus/ NEGATIVE mecA	NEGATIVE	None
29	THR	S. aureus	STERILE	NEGATIVE	NEGATIVE S.aureus/ NEGATIVE mecA	NEGATIVE	None
30	TKR	Staphylococcus capitis	STERILE	NEGATIVE	NA	NEGATIVE	None

THR= Total Hip Replacement; TKR= Total Knee Replacement; TAR= Total Ankle Replacement; NA = Not applicable (specific PCR was only performed in the initial infection was caused by S.aureus); mecA= specific gene found in bacteria, either S. aureus or S. negative coagulase, that determines for resistance to methicillin

We also used Unyvero Multiplex-PCR, which is a new diagnostic system that allows PCR-based detection of implant and tissue infections. This system can detect 23 different pathogens simultaneously and the whole process takes 5 hours as compared to 72 hours with standard cultures. In studies using the Unyvero system, a sensitivity of 80.6% and a specificity of 96% were reported for prosthetic joint infections when compared to tissue cultures [7-8]. The main pathogens involved in tissue and implant infections are included in this commercial molecular system (including *Staphylococcus species (sp.)*, *Streptococcus sp.*, *Pseudomonas sp.*, *Enterococcus sp.*, *Propionibacterium sp.*, *Escherischia sp.* and *Klebsiella sp.*), and it gives a positive result when ≥ 10^4 pathogens are found per ml, depending on the pathogen. In this study, in order to increase the probability of finding pathogens, the spacer sonication fluid was centrifuged to concentrate the number of bacteria in the sample. The Unyvero system seemed an interesting tool as it can analyse simultaneously most frequent pathogens involved in PJI quite quickly, which would allow us to get results earlier than with standard cultures. We tested this system in our case of prosthetic joint infection to see if it could replace some of the current analyses we use.

The results of the multiplex Unyvero PCR were positive for six patients but showed only small quantity of bacteria. The Unyvero system does not indicate a precise number of pathogens but only an estimation. In two cases, the same bacteria that had caused the primary infection was detected. In four cases, a different bacterium than primary infection was detected. In all 6 cases, no re-infection has developed after the end of the antibiotic treatment for the prosthetic joint infection. This showed that this system was not suitable to exclude persistent infection in 2-stage exchange procedures.

Concerning the four cases of infection recurrence which were observed, none had positive PCR for the bacteria involved in their re-infection.

As said above, we have a mean follow-up of 12.8 months, which is a limitation in our study. However, as most infections were caused by Streptococci and Staphyloccoci, we would expect appearance of early infection rather than late infection.

Discussion

Sonication has proven its efficiency in diagnosis of prosthetic joint infection. Trampuz et al showed that sonication fluid cultures have a higher sensibility compared to standard cultures (78.5% versus 60.8%) [5]. However, the sensitivity of sonication fluid cultures decreases slightly to 75% for patients receiving antibiotics within 2 weeks prior to the surgical procedure [5].

Portillo [9] also confirmed the utility of PCR to differentiate prosthetic joint infection and aseptic loosening. However, uncertainty remains concerning the relevance in positive spacer sonication or positive PCR at second stage. Indeed, PCR cannot confirm the presence of viable bacteria in the samples [10]. As PCR is a very sensitive method, it can also show contamination [11].

Concerning spacer sonication, a few studies exist in the literature. In a study from Mariconda et al. 6 of 21 patients had positive sonication cultures, with the same bacteria as found in the first stage surgery. Of the 6 patients with positive sonication cultures, 3 had negative standard cultures [3]. In another study from Nelson et al., 18 of 36 patients had positive sonication cultures. The interval between the two operative stages was a minimum of 12 weeks; a minimum of 6 weeks with intravenous antibiotic administration followed by 6 weeks free of antibiotics. In their study, 11 patients had a re-infection. Of those 11 patients, nine had positive sonication cultures at second stage surgery (31%) but only four cases had positive standard cultures [1]. In a study of 55 patients, Sorli et al. showed 11 cases of subclinical infection at the time of reimplantation. They defined subclinical infection as a patient that showed no clinical signs of acute infection (satisfactory local status and normal CRP), but with either positive sonication or at least 2 positive tissues samples for the same bacteria. 18 patients developed re-infection at 12 months, including 8 of those with subclinical infection [2]. In the group with subclinical infection, they identified the same bacteria involved in the primary infection for 3 of 8 patients.

The cited studies seem to conclude that positive

spacer sonication could be predictive of long-term failure. However, in contrast to our short-interval two-stage exchange procedure, these studies [1-3] describe two-stage procedures with long interval, including a period free of antibiotics before reimplantation. The different treatment approach could explain our results showing only negative standard cultures of the sonicated spacers included in this study. In our experience, concentration of antibiotics present in the sonication fluid is high enough to inhibit the growth of bacteria on cultures. That could be an explanation why our spacer sonication cultures are negative. Based on this hypothesis, PCR analyses were done to increase the chances to detect the presence of bacteria with a non-culture based method.

In our study, all cases that developed a recurrence of infection had negative PCR results for the bacteria involved in the re-infection. Patients with positive PCR results were most often positive for the micro-organism responsible for the primary infection. Although the latter was detected by PCR, these patients did not present reinfection and did not need another surgical procedure. We can thus conclude that a few pathogens originated from the initial infection are not significant and cannot be interpreted as persistent infection in this study.

In our study, the different PCR analyses used did not help to predict which patients will develop a reinfection. PCR showed us either a very small quantity of the bacteria involved in the primary infection, or mixed flora that could be interpreted as contamination. The multiplex PCR system used in this study was faster and less labor-intensive to perform, but remained negative due to very small amount of microorganisms in the sonication fluid. The *S. aureus* specific PCR on the other hand may be too sensitive to diagnose subclinical infection as the low number of pathogens detected would not be clinically significant. With this thought, multiplex PCR, remaining negative, would give us the relevant clinical result, as no clinical persistent infection was detected in our study.

The management of the second step in two stage exchange surgery is still a matter of debate in the treatment of prosthetic joint infection. Currently, there is no consensus to determine the best timing for second stage. Different authors could not determine C-reactive protein (CRP) and ESR cut-off values, allowing for reimplantation, as CRP was even lower in some patients of the re-infection group, compared to the control group [12-14]. Likewise, spacer sonication and PCR at the second stage cannot predict recurrence of infection. Further investigations are needed to identify if PCR could be used to exclude persistence of infection at the second stage of the surgical procedure for prosthetic joint infection.

Conclusions

To our knowledge, this is the first study on relevance of PCR at second stage procedure in prosthetic joint infection. In our study, three different PCR analyses did not improve the bacterial detection and did not help to predict whether the patient will present a recurrence of infection. Prosthetic two-stage exchange with short interval and antibiotic-impregnated spacer is an efficient treatment to eradicate infection as both culture- and molecular-based methods were unable to detect bacteria in spacer sonication fluid after reimplantation.

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IRB/Ethical Committee Approval

This study was approved by the independent local ethics committee (Commission cantonale (VD) d'éthique de la recherche sur l'être humain). Protocol 136/15 on 18th July 2014.

Competing Interests

Sandrine Mariaux and Ulrika Furustrand Tafin have no disclosures.

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